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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/148,973	09/04/1998	J.TIMOTHY GREENAMYRE	PC10023A	4263

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EXAMINER	
BAKER, MAURIE GARCIA	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/148,973	Greenamyre et al
Examiner	**Art Unit**
Maurie G. Baker, Ph.D.	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 28, 2002*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3 and 5-7* is/are rejected.

7) ☒ Claim(s) *4 and 8* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *31*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Please note: The number of Art Unit 1627 has been changed to 1639. Please direct all correspondence for this case to **Art Unit 1639**.

1. The Response filed October 28, 2002 (Paper No. 30) is acknowledged. No claims were amended, added or cancelled. Therefore, claims 1-8 are pending and are examined on the merits in this action.

Status of Rejections

2. The terminal disclaimer filed on October 28, 2002 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,136,812 has been reviewed and is accepted. The terminal disclaimer has been recorded. All of the other previous rejections are maintained and applicant's arguments are addressed following each rejection.

Maintained Rejections
Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al (US 5,670,516; of record) in view of Adams et al (Principles of Neurology; on PTO-1449).

Arnold et al teach a number of neurological disorders such as "drug-induced Parkinson's Disease" and other neurological conditions such as "muscular spasms" and "tardive dyskinesia" (see column 1, line 55 through column 2, line 4). The reference teaches that the "use of a neuroprotective agent, such as an AMPA receptor antagonist, is believed to be useful in treating these disorders" (column 2, lines 4-9). Arnold et al lacks the specific teaching of using an AMPA receptor antagonist to "treat dyskinesia associated with dopamine agonist therapy".

However, it was well known in the art at the time of filing that dyskinesia is a side effect associated with dopamine agonist therapy. For example, Adams et

al when discussing L-dopa treatment of Parkinson's Disease states that one of the "most common and troublesome effects of L-dopa" is dyskinesia (see page 1073, 1st column, 2nd full paragraph). Furthermore, Adams et al teach the combination of L-dopa with a decarboxylase inhibitor (carbidopa or benserazide) which is standard L-dopa therapy and reads on the limitations of the instant claims 2, 3, 6 and 7. See page 1072 of Adams et al, 2nd column, 3rd paragraph.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use an AMPA receptor antagonist (as taught by Arnold et al) to treat dyskinesia associated with dopamine agonist therapy for the following reasons. Adams et al teach that one of the "most common and troublesome effects of L-dopa" is dyskinesia. Arnold et al teaches a number of neurological disorders such as "drug-induced Parkinson's Disease" and other neurological conditions such as "muscular spasms" and "tardive dyskinesia" that can be treated using an AMPA receptor antagonist. Thus, one of ordinary skill would be motivated to use an AMPA receptor antagonist to treat dyskinesia associated with dopamine agonist therapy because Arnold et al teach that blocking AMPA receptors is an effective way to treat neurological disorders, such as dyskinesias and Adams et al teach that one of the "most common and troublesome effects of L-dopa" is dyskinesia.

Response to Arguments

6. Applicant's arguments filed October 28, 2002 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

7. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner maintains that the *combined* teachings of the cited references render the claimed invention obvious. Again, from the rejection above, Adams et al teach that one of the "most common and troublesome effects of L-dopa" is dyskinesia. Arnold et al teaches a number of neurological disorders such as "drug-induced Parkinson's Disease" and other neurological conditions such as "muscular spasms" and "tardive dyskinesia" that can be treated using an AMPA receptor antagonist. Thus, one of ordinary skill would be motivated to use an AMPA receptor antagonist to treat dyskinesia associated with dopamine agonist therapy because Arnold et al teach that blocking AMPA receptors is an effective way to treat neurological disorders, such as dyskinesias and Adams et al teach that one of the "most common and troublesome effects of L-dopa" is dyskinesia.

8. Also, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references.

Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

9. Specifically, applicant argues that it would not be obvious to use AMPA receptor antagonists for the treatment of the specific condition specified in the claims. However, the examiner's position is that the teachings referred to above (paragraph 7) are strong motivation. Also, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial result of the combination of references is treating one of the "most common and troublesome effects of L-dopa" (i.e. dyskinesia, as taught by Adams et al).

10. Applicant also states that "[n]othing in the prior art points to the possibility of using an AMPA receptor antagonist to treat such dopamine agonist-induced dyskinesias". The examiner respectfully disagrees as the combination of the teachings of the Arnold and Adams references does indeed point to such an option. "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344

(CCPA 1968). Again, as stated in the rejection, the examiner's position is that one of ordinary skill would be motivated to use an AMPA receptor antagonist to treat dyskinesia associated with dopamine agonist therapy because Arnold et al teach that blocking AMPA receptors is an effective way to treat neurological disorders, such as dyskinesias and Adams et al teach that one of the "most common and troublesome effects of L-dopa" is dyskinesia.

11. Applicant states that the "invention claimed in the present application of using an AMPA receptor antagonist to inhibit dopamine agonist-induced dyskinesias was unexpected and contraindicated by the prior art" (Response, page 3). The examiner does not deem this to be sufficient support for unexpected results. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results... See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence"). Moreover, applicant's arguments do not rise to the level of factual evidence. See MPEP § 716.01(c): The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Lastly, any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (In

MPEP § 716.02). Please note that any evidence filed After Final will ***not*** be considered unless good and sufficient reasons why it was not earlier presented are shown.

12. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stella et al (Annals of Neurology, 1996; of record) in view of Arnold et al (US 5,670,516; of record) and further in view of Adams et al (Principles of Neurology; on PTO-1449).

Stella et al teach that antagonists of the NMDA receptor "reverse levodopa-induced motor fluctuations in animal models of Parkinson's disease" (see Abstract). The reference teaches administering the standard therapy for Parkinson's disease, i.e. combination of L-dopa with a decarboxylase inhibitor (benserazide) and that this induced "moderately severe dyskinesias" (page 575, 1st column under 'Drug Administration'). Stella et al teach that administration of an antagonist of the NMDA receptor "substantially reduced" or "abolished" certain dyskinesias resulting from L-dopa therapy, thus providing "an ameliorative effect on levodopa-induced dyskinesias" (see page 577, 1st column under 'Discussion'). Stella et al lack the teaching of using an AMPA receptor antagonist.

However, Arnold et al teach a number of neurological disorders such as "drug-induced Parkinson's Disease" and other neurological conditions such as "muscular spasms" and "tardive dyskinesia" (see column 1, line 55 through column 2, line 4). The reference teaches that the "use of a neuroprotective agent,

such as an AMPA receptor antagonist, is believed to be useful in treating these disorders" (column 2, lines 4-9). Arnold et al teach that NMDA and AMPA receptors are subtypes of the same receptor (see column 1, lines 25-33).

Also, it was well known in the art at the time of filing that dyskinesia is a side effect associated with dopamine agonist therapy. For example, Adams et al when discussing L-dopa treatment of Parkinson's Disease states that one of the "most common and troublesome effects of L-dopa" is dyskinesia (see page 1073, 1st column, 2nd full paragraph). Furthermore, Adams et al teach the combination of L-dopa with a decarboxylase inhibitor (carbidopa or benserazide) which is standard L-dopa therapy and reads on the limitations of the instant claims 2, 3, 6 and 7. See page 1072 of Adams et al, 2nd column, 3rd paragraph.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use an AMPA receptor antagonist (as taught by Arnold et al) in the method of Stella et al to treat dyskinesia associated with dopamine agonist therapy for the following reasons. Adams et al teach that one of the "most common and troublesome effects of L-dopa" is dyskinesia. Stella et al specifically teach that antagonists of the NMDA receptor produce "an ameliorative effect on levodopa-induced dyskinesias". Arnold et al teaches a number of neurological disorders such as "drug-induced Parkinson's Disease" and other neurological conditions such as "muscular spasms" and "tardive dyskinesia" that can be treated using an AMPA receptor antagonist. Thus, one of ordinary skill would be motivated to use an AMPA receptor antagonist to treat dyskinesia

associated with dopamine agonist therapy because Arnold et al teach that blocking AMPA receptors is an effective way to treat neurological disorders, such as dyskinesias and Adams et al teach that one of the "most common and troublesome effects of L-dopa" is dyskinesia. Furthermore, since Stella et al teach that antagonists of the NMDA receptor produce "an ameliorative effect on levodopa-induced dyskinesias" and Arnold et al teach that NMDA and AMPA receptors are subtypes of the *same receptor* then it would be obvious to one of ordinary skill to substitute an antagonist of the AMPA receptor for the antagonist of the NMDA receptor taught by Stella et al.

Response to Arguments

13. Applicant's arguments filed October 28, 2002 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

14. Please see paragraphs 6-11 above. With respect to applicant's arguments specifically regarding the rejection above, the examiner would like to first note that it is indeed the Papa and Chase article that was being referred to in the rejection (first author Stella M. Papa) as pointed out by applicant.

15. Applicant argues that since there are numerous reports in the literature that AMPA and NMDA receptor antagonists have very different physiological effects, the observation that an NMDA receptor antagonist reduced dopamine agonist-induced

dyskinesias "would not have led to the deduction of the utility of an AMPA receptor antagonist to treat dopamine agonist-induced dyskinesias" (Response, page 3). The examiner respectfully disagrees. As stated in the rejection, one of ordinary skill would be motivated to use an AMPA receptor antagonist to treat dyskinesia associated with dopamine agonist therapy because Arnold et al teach that blocking AMPA receptors is an effective way to treat neurological disorders, such as dyskinesias and Adams et al teach that one of the "most common and troublesome effects of L-dopa" is dyskinesia. Furthermore, since Stella et al teach that antagonists of the NMDA receptor produce "an ameliorative effect on levodopa-induced dyskinesias" and Arnold et al teach that NMDA and AMPA receptors are subtypes of the *same receptor* then it would be obvious to one of ordinary skill to substitute an antagonist of the AMPA receptor for the antagonist of the NMDA receptor taught by Stella et al.

16. Regarding the other references discussed in the Response, it is noted that the rejection is only based on Stella (Papa and Chase), Adams and Arnold. Also, the test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991). The examiner maintains that the combined teachings of the Stella (Papa and

Chase), Adams and Arnold references would render the claimed invention *prima facie* obvious to one of ordinary skill in the art.

Status of Claims/Conclusion

17. No claims are allowed. However, claims 4 and 8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is

(703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

20. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.
February 21, 2003

MAURIE GARCIA BAKER, Ph.D.
PRIMARY EXAMINER